UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte Gregory M. Fahy

Appeal No. 2006-0148
Application No. 09/933,309

ON BRIEF

Before MILLS, GRIMES, and GREEN, Administrative Patent Judges.

GRIMES, Administrative Patent Judge.

DECISION ON APPEAL

This appeal involves claims to a method of preventing rejection of a transplanted organ or tissue. The examiner has rejected the claims on the basis that they are indefinite and nonenabled. We have jurisdiction under 35 U.S.C. § 134. We reverse.

Background

"Of all the developments in modern immunology that promise to make the rejection of transplanted cells, tissues, and organs obsolete, the most exciting is the technique of intrathymic transplantation pioneered by Naji et al. . . . The method involves first transplanting a biopsy sample of the graft into the thymus of the recipient and then transplanting the graft itself after a predetermined time. The presence of the

intrathymic biopsy renders the host tolerant to the graft itself, either by eliminating or anergizing immune cells that attack the biopsy in the thymus. . . . The main problem with this method is that it requires a functioning thymus gland of significant mass in order to be effective. The human thymus begins to involute before the age of 20 and becomes severely atrophied by the age of 40." Specification, pages 2-3.

The specification discloses that "[t]he concurrent administration of human growth hormone or an HGH releaser and DHEA [dehydroepiandrosterone] . . . surprisingly reverses thymic involution in older individuals and in others with thymic insufficiency." Pages 14-15. "By regenerating the previously atrophied thymus, this coadministration of HGH and DHEA allows intrathymic transplantation in elderly or involuted individuals as a route to permanent grafting of tissues and organs without immunosuppression and without rejection." Page 15.

Discussion

1. Claims

Claims 16-22 and 32-34 are pending and on appeal. Claim 16 is the only independent claim and reads as follows:

16. A method for transplanting organs and grafting tissue into a patient comprising steps of:

restoring immune system function by regenerating the patient's involuted thymus;

injecting the immunological equivalent of the tissue or organ to be transplanted into the patient, into the regenerated thymus (or, in the case of bone marrow cells, peripherally); and

then transplanting said organ or grafting said tissue.

2. Definiteness

The examiner rejected claim 16 under 35 U.S.C. § 112, second paragraph, as indefinite. The examiner cited two bases for this rejection. First, the examiner concluded that

> Claim 16 is indefinite because the method comprises regenerating the patient's involuted thymus, but the steps of regenerating the involuted thymus have not been taught. . . . The claim does not set forth any steps involved in the method/process of regenerating an involuted thymus. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Examiner's Answer, page 4.

We will reverse this basis of the rejection. The examiner appears to be relying on Ex parte Erlich, 3 USPQ2d 1011 (BPAI 1986), for the cited rule. The holding of that case, however, does not apply here. The relevant claims in Erlich recited a "process for using monoclonal antibodies [specific for human fibroblast interferon] to isolate and purify human fibroblast interferon" or a "process for using monoclonal antibodies [specific for human fibroblast interferon] to identify human fibroblast interferon." Id. at 1012. The claims had been rejected under 35 U.S.C. § 112, second paragraph, as incomplete because they did not recite any steps. Id. at 1017. The Board affirmed, holding that "a method claim should at least recite a positive, active step(s) so that the claim will 'set out and circumscribe a particular area with a reasonable degree of precision and particularity' and make it clear what subject matter these claims encompass, as well as making clear the subject matter from which others would be precluded." Id. (citations omitted).

In contrast to the claims in Erlich, instant claim 16 recites the positive, active steps of "regenerating [a] patient's involuted thymus; injecting the immunological equivalent of the tissue or organ to be transplanted . . .; and then transplanting said organ or grafting said tissue." Therefore, the claim is not indefinite under the rationale of Ex parte Erlich.

The examiner also rejected claim 16 "because the term 'immunological equivalent' is a relative term which renders the claim indefinite. The term 'immunological equivalent' is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention." Examiner's Answer, page 4.

Appellant argues that "[t]hose having ordinary skill in the art would not regard the expression 'immunological equivalent' as a relative term. A material either is or is not the immunological equivalent of the organs and/or tissue grafted into the patient. In other words, the material either does or does not induce an immunological effect equivalent to the tissue or organ to be transplanted." Appeal Brief, page 6.

We will reverse this basis of the rejection as well. The specification states that

> [a]fter thymic regeneration, the thymus should be imaged . . . to verify regeneration and thymic location. . . . At this time, a surgeon skilled at thymic biopsy retrieval injects into the thymus an appropriate sample of the tissue or organ to be transplanted later, or injects any other donor-specific cells or antigens (for example bone marrow cells) that are the immunological equivalent of the tissue itself in stimulating deletion or anergy of the cells otherwise responsible for later rejecting the transplanted tissue or organ.

Page 15. [Emphasis added.]

Thus, the specification makes clear that an "immunological equivalent" of a transplanted organ or tissue is a donor-specific cell or antigen that stimulates deletion or anergy of the immune system cells that would otherwise cause rejection of the transplanted organ or tissue. The specification states that one example of an immunological equivalent is "bone marrow cells." In our view, "the claims, read in light of the specification, reasonably apprise those skilled in the art and are as precise as the subject matter permits," Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94-95 (Fed. Cir. 1987), and therefore comply with the second paragraph of 35 U.S.C. § 112.

3. Enablement

The examiner rejected claims 16-22 and 32-34 under 35 U.S.C. § 112, first paragraph, on the basis that the claimed method is not enabled by the specification's disclosure. The examiner reviewed several of the references submitted by Appellant to show thymic regeneration and lack of rejection following intrathymic injection of antigen (Examiner's Answer, pages 5-6) and concluded that, "[w]hile the literature submitted by Appellant teaches regeneration of age-involuted thymus, the experiments were only executed in rats, there was no significant improvement of cellular immune function and there were harmful side effects (reduced testosterone concentrations, hepatic tumors)." Id., page 7.

The examiner also faulted the level of disclosure in the specification, arguing that:

• "[t]he specification does not provide guidelines to determine thymic atrophy or involution" (Examiner's Answer, page 7);

• "[t]he disclosure does not provide immunological or endocrine assays or employ experiments such as magnetic resonance imaging or morphology studies, which would discern that a thymus has been regenerated" (id.);

• "[t]he specification provides no guidance or working examples for intrathymic injection" (id.); and

• "[t]he specification fails to teach or disclose working examples for transplanting an organ or grafting of tissue" (id.).

The examiner concluded that

> [d]ue to the large quantity of experimentation necessary to regenerate an involuted thymus, administer an intrathymic injection and transplant an organ or tissue, the lack of direction/guidance presented in the specification regarding same, the absence of working examples directed to same, the complex nature of the invention, and the state of the prior art which establishes the unpredictability of intrathymic injections and organ/graft transplants, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Id., page 8.

Appellant argues that "the specification expressly teaches techniques for regenerating an involuted thymus," and that the examiner has conceded that at least the Greenstein[1] and McCormick[2] references show regeneration of an involuted thymus. Appeal Brief, page 14. Appellant also argues that

> [a] surgeon skilled at thymic biopsy retrieval (one of ordinary skill in the art) would know how to achieve the intrathymic injection without undue experimentation, and a skilled transplant surgeon would know how to transplant an organ or graft a tissue without undue experimentation. Accordingly, each of the individual steps of the claimed method may be achieved by those having ordinary skill in the art without undue

[1] Greenstein et al., "Regeneration of the thymus in old male rats treated with a stable analogue of LHRH," J. Endocr., Vol. 112, pp. 345-350 (1987).
[2] McCormick et al., "A murine model for regeneration of the senescent thymus using growth hormone therapy," AGING: Immunology and Infectious Disease, Vol. 3, pp. 19-26 (1991).

> experimentation. . . . Normally, if all of the steps of a claimed process are enabled, the claimed process is enabled.

Id., page 15.

"When rejecting a claim under the enablement requirement of section 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification" In re Wright, 999 F.2d 1557, 1561-62, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

"[E]nablement requires that the specification teach those in the art to make and use the invention without 'undue experimentation.' In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). That some experimentation may be required is not fatal; the issue is whether the amount of experimentation required is 'undue.'" In re Vaeck, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991) (emphasis in original). "The key word is 'undue,' not 'experimentation.'" In re Angstadt, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976).

In this case, the claims are directed to a method comprising three steps: regenerating an involuted thymus, injecting into the regenerated thymus a sample of the tissue or organ to be transplanted, and transplanting a tissue or organ. The examiner has pointed out that "[t]he specification provides no guidance or working examples for intrathymic injection," and "[t]he specification fails to teach or disclose working examples for transplanting an organ or grafting of tissues." Examiner's Answer, page 7.

It is unclear from the statement of rejection in the Examiner's Answer how much weight the examiner puts on the specification's lack of working examples of intrathymic

injection and organ transplant. The examiner has conceded that "transplanting said organ or grafting said tissue is enabled in humans," Examiner's Answer, page 28, so that aspect of the claimed method would not appear to involve any more than routine experimentation. The examiner has also conceded that intrathymic injection is known in the art with respect to laboratory animals (citing Odorico[3]), although "the thymus in the rat was not regenerated before the intrathymic injection." Examiner's Answer, page 44.

To the extent that the examiner relies on the experimentation involved in intrathymic injection and organ transplantation as contributing to the conclusion of nonenablement, we disagree. The examiner has conceded that organ transplantation is enabled in humans, and the record appears to show that intrathymic injection was practiced routinely by those skilled in the art.

Odorico, for example, discloses "[i]ntrathymic (i.t.) inoculation of donor splenocytes . . . after upper median sternotomy and direct visualization of both lobes of the thymus." Page 1104 ("Pretransplant recipient preparation"). Similarly, Perico[4] reports that "[g]lomeruli were freshly isolated from the right kidney of rat donors. . . . The purity of the isolated glomeruli was determined microscopically. . . . The glomeruli were then counted and injected into the thymus of Lewis rats." Page 1065 ("Isolated Glomeruli"). Neither reference provides any detailed guidance on how to carry out an intrathymic injection. Odorico and Perico thus provide evidence that those skilled in the art did not require detailed guidance in order to carry out an intrathymic injection.

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[3] Odorico et al., "Promotion of rat cardiac allograft survival by intrathymic inoculation of donor splenocytes," Transplantation, Vol. 55, pp. 1104-1107 (1993).
[4] Perico et al., "Thymus-mediated immune tolerance to renal allograft is donor but not tissue specific," Journal of the American Society of Nephrology, Vol. 2, pp. 1063-1071 (1991).

The instant specification states that

> [a]fter thymic regeneration, the thymus should be imaged (preferably by magnetic resonance imaging, though other methods are also acceptable) to verify regeneration and thymic location. . . . At this time, a surgeon skilled at thymic biopsy retrieval injects into the thymus an appropriate sample of the tissue or organ to be transplanted later.

Page 15, lines 18-23. The examiner has not provided a reasoned explanation of why this level of guidance is inadequate to enable those skilled in the art to practice intrathymic injection without undue experimentation. A conclusory statement that "intrathymic injection [is an] unpredictable and undeveloped art[ ]" (Examiner's Answer, page 23) is not sufficient.

Thus, the only step in the claimed method that might involve something more than routine experimentation appears to be the first step: "restoring immune system function by regenerating the patient's involuted thymus." The examiner has argued that "[w]hile the literature submitted by Appellant teaches regeneration of age-involuted thymus, the experiments were only executed in rats, which are not representative of the scope of the claims, there was no significant improvement of cellular immune function and there were harmful side effects (reduced testosterone concentrations, hepatic tumors). . . . One of the limitations of the instant claims is restoring immune function." Examiner's Answer, page 19.

Appellant argues that the specification discloses specific methods that result in regeneration of a patient's involuted thymus. See the Appeal Brief, page 14. Appellant also argues that he "has submitted evidence proving that the disclosed HGH therapy is effective for almost doubling the functional thymic mass of Appellant's own thymus.

Those having ordinary skill in the art would expect that a doubling of functional thymic mass would result in an increase in thymic function." Appeal Brief, page 16.

The evidence referred to by Appellant is apparently the declaration he submitted under 37 CFR § 1.132 (originally filed August 29, 2003). The declaration describes an experiment in which Appellant administered to himself hGH and DHEA over a period of 36 days, and the results of magnetic resonance imaging (MRI) before and after the period of hGH and DHEA administration. The declaration states that the MRI "images showed a combination of visually white . . . mass indicative of adipose tissue substitution for lymphoid tissue, a typical observation for this age range, and visually gray . . . mass, representing lymphoid or functioning thymic mass. However, the [after-treatment] set of images distinctly and consistently shows more total thymic cross-sectional area and more gray thymic cross-sectional area, and a definite darkening of some gray regions following treatment." Page 2 ("Results").

The examiner did not dispute the accuracy of the Fahy declaration but argued that an increase in thymic mass does not necessarily mean an increase in thymic function. See the Examiner's Answer, page 23: "Goff[5] . . . states a change (or lack of change) in thymic morphology does not prove increased or decreased thymic function; immunological or endocrine function must be assessed. Furthermore, the Fahy Declaration fails to demonstrate that immune system function has been restored."

We do not agree that Goff provides evidence contrary to the evidence in the Fahy declaration. Goff teaches that the "thymus gland has an endocrine component,

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[5] Goff et al., "Growth hormone treatment stimulates thymulin production in aged dogs," Clin. Exp. Immunol., Vol. 68, pp. 580-587 (1987).

the thymic epithelial cells, which produce several well-characterized peptides. . . . One such peptide is thymulin." Page 580, last paragraph. Goff reports the results on thymus morphology and function of administering bovine growth hormone (bGH) to middle-age and old-age dogs. Goff states that "a change (or lack of change) in thymic morphology does not prove increased or decreased thymic function; immunological or endocrine function must also be assessed. The present results indicate that bGH treatment did stimulate the endocrine function of the thymus as measured by its thymulin production." Page 585, third full paragraph. See also page 586, second full paragraph: "We have demonstrated that GH treatment not only improves thymic morphology in middle-aged dogs, but also thymic function as evidence by increases in thymulin levels even in the oldest dogs studied. The results suggest that exogenous GH may be useful for restoration of some immune functions in aged individuals."

In our view, the evidence provided by Goff supports, rather than contradicts, the Fahy declaration. The Fahy declaration states that MRI images of the thymus showed a combination of white and gray mass, and that the white mass was "indicative of adipose tissue substitution for lymphoid tissue," while the gray mass "represent[ed] lymphoid or functioning thymic mass." Page 2. The declaration presents a comparison of total thymus area and total gray area before and after growth hormone treatment. Table 1. Relying on certain assumptions, the declaration concludes that "[t]he percent increase in total thymic lymphoid (functional) mass induced by the Fahy art was 92%." Page 4, first full paragraph.[6]

[6] The examiner noted but did not take issue with the declaration's conclusion. See the Examiner's Answer, page 23, lines 2-4.

Like the experiment described in the Fahy declaration, the experiment described by Goff analyzes the effect of growth hormone (bGH) administration on the thymus. Goff evaluates changes in both thymus morphology and function (specifically, thymulin production). Goff concludes that in middle-aged but not old-age dogs, growth hormone "treatment resulted in rejuvenation of thymic morphological features," abstract, and "bGH-treated dogs had significantly greater plasma thymulin concentrations than BSA-[bovine serum albumin-]treated controls regardless of age." Page 584.

Thus, both the Fahy declaration and Goff conclude that growth hormone treatment produces an increase in thymus function. While the Fahy declaration bases its conclusion on the results of MRI imaging, while Goff bases its conclusions on assays for thymulin production, the fact that both experiments reached similar conclusions, by different analytical methods, is more conclusive than either experiment alone.

The examiner cites McCormick[7] as evidence that an increase in thymus mass does not necessarily indicate an increase in thymus function. See the Examiner's Answer, page 19: "McCormick teaches that regeneration of an age-involuted thymus can be accomplished in rats [sic, mice] using growth hormone, however, there was no significant improvement of cellular immune function."

We do not find that the evidence provided by McCormick outweighs the evidence provided by Goff and the Fahy declaration. As the examiner noted, McCormick concludes that growth hormone treatment of mice increased thymus mass and restored morphological integrity of the thymus, although McCormick does not report any

[7] Supra, note 2.

significant improvement of cellular immune function. See, e.g., the abstract. McCormick did not, however, conclude that growth hormone treatment had no effect on thymus function. Rather, McCormick stated that

> [o]ur results would seem to indicate that the rejuvenation of the senescent cellular immune response is not achieved as quickly as the rejuvenation of the thymus gland. The thymus regained much of its normal young morphology after 8 weeks of growth hormone treatment but cellular immune function did not recover as quickly. This can be explained in either of two ways. First, it may be due to the time lag in the seeding of the peripheral lymphoid organs with newly matured and normal functioning thymocytes from the rejuvenated thymus. Alternatively, it may be that the thymus factors responsible for maintaining the vigor of the cellular immune response have not been present for a long enough period of time to restore peripheral lymphocytes to normal functioning levels.

Paragraph bridging pages 23 and 24.

Thus, while McCormick observed no increase in thymus function during the time period of the disclosed experiment, the researchers reported that they expected increased thymus function because of "the rejuvenation of the thymus gland." McCormick suggests that improved function was expected, even though it was not observed as quickly as improved morphology.

None of the results reported by McCormick directly contradict the conclusions reached by Goff and the Fahy declaration – that growth hormone treatment improves thymus function. As discussed above, the results reported by Goff and in the Fahy declaration reinforce each other and therefore are entitled to more weight collectively than McCormick's negative results (which even McCormick tries to explain away). We find that the preponderance of the evidence in the record favors Appellant's position that growth hormone treatment is likely to produce an increase in thymus function.

The examiner also cites McCormick, as well as Greenstein,[8] as evidence that growth hormone therapy results in side effects that could interfere with the successful practice of the claimed process. See, e.g., the Examiner's Answer, pages 7 and 19-20.

We do not agree with the examiner's reasoning. First, the examiner has not presented evidence or sound scientific reasoning to show that the hepatic tumors or reduced testosterone levels reported by McCormick and Greenstein, respectively, would be expected to have any effect on thymus function. The examiner has conceded that "the patent laws do not require that any invention must be free of all drawbacks, side effects and complications." Examiner's Answer, page 33. We agree. See, e.g., CFMT, Inc. v. Yieldup Int'l Corp., 349 F.3d 1333, 1338, 68 USPQ2d 1940, 1944 (Fed. Cir. 2003) ("Title 35 does not require that a patent disclosure enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment absent a claim limitation to that effect."); In re Brana, 51 F.3d 1560, 1567, 34 USPQ2d 1436, 1442 (Fed. Cir. 1995) ("'[O]ne who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, even though it may eventually appear that the compound is without value in the treatment of humans.'").[9]

The examiner has not provided a reasonable explanation of why the side effects observed by McCormick and Greenstein would have been expected to affect the function of the thymus gland. Therefore, the examiner has not adequately explained why those side effects would be a factor in the enablement of the claimed method.

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[8] Supra, note 1.
[9] Although the Brana court referred to "useful[ness]," the rejection on appeal was for lack of enablement. See 51 F.3d at 1564, 34 USPQ2d at 1439.

Summary

The examiner has not adequately shown that those of ordinary skill in the art would not have understood the meaning of the claims, or that undue experimentation would have been required to practice the claimed method. Therefore, we reverse the rejections under the first and second paragraphs of 35 U.S.C. § 112.

REVERSED

Demetra J. Mills)
Administrative Patent Judge)
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Eric Grimes) BOARD OF PATENT
Administrative Patent Judge)
) APPEALS AND
) INTERFERENCES
Lora M. Green)
Administrative Patent Judge)

EG/dym

Price, Heneveld, Cooper, Dewitt & Litton, LLP
695 Kenmoor, S.E.
P.O. Box 2567
Grand Rapids, MI 49501